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ORIGINAL ARTICLE

Nomograms in Hepatectomy Patients with Hepatitis B Virus-Related Hepatocellular Carcinoma

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Abstract

Background Several conventional staging systems use tumor count as a variable for tumor classification; however, most conventional staging systems for hepatocellular carcinoma (HCC) are not specifically constructed for surgically treated patients. The aim of this study was to create a prognostic nomogram based on patient' clinical and pathological features for predicting individual patient survival after liver resection as a primary therapy for solitary hepatitis B virus (HBV)-related HCC.

Methods This study included patients who underwent curative liver resection for preoperative treatment-naïve HBV-related HCC between April 2007 and September 2014. All data were collected prospectively.

Results A nomogram was generated for HCC recurrence and mortality in 420 hepatectomy patients. HCC recurrence was closely associated with the following factors: increased alkaline phosphatase, low albumin, increased protein induced by vitamin K absence/antagonism-II (PIVKA-II), multiple tumors, tumor hemorrhage, portal vein tumor thrombosis, intrahepatic metastasis, and free resection margin (< 4 cm). Increased alanine transaminase, tumor size ≥ 5 cm, and multiple tumors were predisposing factors for death. Nomograms using those factors had good calibration and discrimination abilities with *C*-indexes of 0.712 and 0.819, respectively.

Conclusions Our results suggest that prognostic nomograms in hepatectomy patients with HBV-related HCC can more precisely estimate postoperative survival of individual HBV-related HCC patients.

Keywords Nomogram · Hepatectomy · Tumor recurrence · Survival · Prognosis

Abbreviations

HCC	Hepatocellular carcinoma
AFP	Alpha-fetoprotein
PIVKA-II	Proteins induced by vitamin K antagonist-II
CRP	C-reactive protein
HBV	Hepatitis B virus
RFS	Relapse-free survival
PS	Patient survival
ICG-R15	Indocyanine green retention rate at 15 min
HBsAg	Hepatitis B surface antigen

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PET	Positron emission tomography
RFA	Radiofrequency ablation
TACE	Transarterial chemoembolization
ROC	Receiver operating characteristic
CI	Confidence interval
HR	Hazard ratio
C-index	Concordance index
AST	Aspartate transaminase
ALT	Alanine transaminase
ALP	Alanine phosphatase

Introduction

Liver resection is recommended as a curative treatment for patients with solitary liver cancer and very well-preserved liver function.[1,2] However, only about 20% of patients with hepatocellular carcinoma (HCC) are eligible for surgical resection.[3] The survival rate for HCC patients increases after curative liver resection when surgery has been appropriately selected and postoperative treatment proceeds successfully. Limitations of curative liver resection success lead to potential HCC recurrence due to residual cancer in the remnant liver or the possibility of de novo HCC recurrence by HBV.[4]

HCC staging is not universally established and remains controversial. Thus, there have been many more proposed staging systems for HCC than for other malignant tumor types. Additionally, tumor presence and underlying cirrhosis require a multidisciplinary approach by a treatment team made up of hepatologists, surgeons, radiologists, oncologists, and radiation oncologists. Several conventional staging systems use tumor size and number as variables for tumor classification.[1,5] However, most conventional staging systems for HCC are not constructed for hepatectomy patients and are based on preoperative data. Therefore, accurate prediction of patient prognosis after surgery is difficult.

Nomograms have been developed and presented as alternative or novel predictive systems for various malignancies.[6,7] Nomograms enable personalized prediction according to an individual patient's characteristics, including prediction of tumor recurrence. This personalized knowledge improves a physician's ability to guide and counsel patients about their disease. Nomogram research has demonstrated ability to predict recurrence, survival, and distant metastasis after various treatments for HCC.[8–11]

Currently, there are no nomograms that can predict hepatectomy outcomes in treatment-naïve hepatitis B virus (HBV)-related HCC patients. Thus, we constructed a simple and clinically relevant nomogram to predict HCC recurrence and survival in patients with treatment-naïve HBV-related HCC.

Materials and Methods

Patients

Data from patients who underwent liver resection for pathologically proven HBV-related HCC at the Samsung Medical Center in Seoul between April 2007 and September 2014 were prospectively collected and retrospectively reviewed. The study was approved by the Institutional Review Board (IRB) at Samsung Medical Center (SMC-2017-04-040), which also exempted the study from requiring informed consent.

The inclusion criteria were (1) histologically confirmed HBV-related HCC; (2) performance status score of 0 to 1;[12] (3) no evidence of extrahepatic metastasis; (4) no history of other malignancies; (5) curative resection; and (6) HCC based on preoperative radiologic images. Exclusion criteria were (1) etiology other than HBV; (2) mixed HCC and cholangiocarcinoma on pathology; (3) age < 18 years; (4) palliative hepatic resection; (5) concurrently intraoperative RFA during surgical resection; (6) fibrolamellar HCC; (7) death caused by severe surgical complications; (8) missing or incomplete data; (9) history of preoperative locoregional therapies such as liver resection, transarterial chemoembolization, radiofrequency ablation, or radiation; or (10) loss to follow-up after hepatectomy. Demographic information, preoperative laboratory data, and pathologic data from electronic medical records were retrospectively reviewed.

None of the patients in either group received postoperative adjuvant therapy before recurrence. All patients with HBV-related HCC received antiviral therapy after liver resection.

Preoperative Examination and Indications for Hepatectomy

Each patient underwent conventional liver function tests and measurement of the indocyanine green retention rate at 15 min (ICG-R15). Hepatitis B virus screening was based on presence of the hepatitis B surface antigen (HBsAg). The levels of alpha-fetoprotein (AFP) and protein induced by vitamin K absence/antagonism-II (PIVKA-II) were also measured in all patients. Preoperative chest X-ray, electrocardiogram (ECG), cardiac echogram, enhanced liver CT, liver MRI, and preoperative positron emission tomography (PET)/CT were performed to exclude cardiopulmonary diseases and to confirm the HCC diagnosis and suitability of a surgical approach. The HCC diagnosis was confirmed based on current American, European, and Korean practice guidelines.[13,14]

Selection criteria for the liver resection procedure were tumor location and extent, liver function, ICG test, and future liver remnant volume. In patients without ascites and with normal bilirubin level, ICG-R15 was the main resectability determinant. Child–Pugh classes B and C, severe comorbidity,

and distant metastases were considered contraindications for liver resection.

Surgery and Pathology

Surgical and pathological procedures used after liver resection were previously described, [4,15] and standard operative techniques for hepatectomy were used. Postoperative histological assessment and reporting included maximal tumor size, tumor number, encapsulation, tumor hemorrhage, tumor grade, tumor necrosis, portal vein tumor thrombosis (PVTT), bile duct tumor thrombosis (BDTT), intrahepatic metastasis, multicentric occurrence, microvascular invasion, serosal involvement, tumor-free resection margin, and cirrhosis. Intrahepatic metastasis and multicentric occurrence were defined based on guidelines from the Liver Cancer Study Group of Japan.[16] An HCC histologic grade was assigned according to the Edmonson–Steiner system as well differentiated (grade I), moderately differentiated (grade II), or poorly differentiated (grades III and IV).[17]

Surveillance after Surgical Resection

Surveillance procedures after liver resection were previously described.[18] All patients were checked every 2 or 3 months in the second postoperative year and every 6 months in subsequent years. Radiologic evaluations were performed every 3 months or when recurrence was suspected. HCC recurrence was defined based on imaging confirmations. Overall survival (OS) was defined as the interval death date or the last follow-up date from the hepatectomy date, while relapse-free survival (RFS) was defined as the interval from the recurrence date or the last follow-up date from the hepatectomy date. Follow-up time was the length of time from surgery to final follow-up or death.

Statistical Analysis

The primary outcome measures were RFS and OS. Continuous variables are described as median and range. Categorical variables are expressed as number with percentage of subjects. The p values for AST, ALT, ALP, and albumin could not significantly predict HCC recurrence or mortality, but p value estimates were all < 0.1. The p values for AFP and PIVKA-II were significant, but their HRs and 95% confidence intervals were both 1.000 and 1.000–1.000, respectively. Thus, we changed these continuous variables to binary categorical variables. Fisher's exact test was conducted to evaluate differences in the frequencies of categorical variables between the groups. The Mann-Whitney U test was conducted to evaluate differences in continuous variables between the two groups.

Factors that were significant ($p < 0.05$) for predicting RFS or OS in univariate survival analysis were selected for inclusion in a multivariate survival model using the stepwise method. Confidence intervals (CIs) and hazard ratios (HRs) were calculated. β-coefficients from a final Cox model were used to construct the nomogram. The proportional hazards assumption was verified by testing time correlations and examining residual plots. A nomogram was formulated based on Cox model results.

The nomogram was internally validated based on 1000 bootstrap resamples of the same size as the original data, because our sample size was relatively small. For internal validation, the discriminative ability and calibration of the nomogram were examined with a concordance index (C-index) and calibration plot, respectively.[19]

All tests were two-tailed, and statistical significance was defined as $p < 0.05$.

Results

Baseline Characteristics

In total, 420 patients who underwent curative hepatic resection and who met the inclusion criteria were included in this study. The baseline characteristics of all patients are summarized in Table 1. Nearly 79.3% of the patients were male, and the mean age was 53.9 ± 9.2 years. All patients were Child–Pugh class A and remained HBsAg positive throughout the study. One hundred ninety-three patients (46.0%) had positive HBV DNA in the preoperative period, and the median HBV DNA level was 68 IU/mL (range, 9–170,000,000 IU/mL). Median AFP and PIVKA-II levels were 18 mg/dL (range, 1.3–200,000 mg/dL) and 79 mAU/mL (range, 8–75,000 mAU/mL), respectively. The mean ICG-15 was 10.1 ± 5.5%. Nearly 60% of patients were positive on preoperative PET/CT.

Perioperative and Pathologic Characteristics

Patients' perioperative and pathologic characteristics are outlined in Table 1. No patients had lymph node metastases in preoperative images or pathologic reports, 42.2% of patients underwent major liver resection, and 16.2% of patients underwent laparoscopic liver resection. The median tumor size was 3.5 cm (range, 0.3–16.5 cm). Most patients (90.2%) showed evidence of encapsulation, 44.3% of patients showed the evidence of tumor necrosis, and the median pathologic tumor necrosis in patients with tumor necrosis was 50%. The incidence of PVTT and microvascular invasion was 7.9% ($n = 33$) and 56.7% ($n = 238$), respectively. Finally, 39.8% of patients had background liver cirrhosis.

Table 1 Baseline characteristics

Preoperative	
Gender (male)	333 (79.3%)
Age (years)	53.9 ± 9.2
Positive HBV DNA	193 (46.0%)
Neutrophil count (/μL)	2997 (670–10,594)
Lymphocyte count (/μL)	1775 (410–4000)
NLR	0.6 ± 0.3
NMR	0.1 ± 0.1
Hemoglobin (g/dL)	14.3 ± 1.7
Platelet (/μL)	166,500 ± 64,200
AST (U/L)	30 ± 29
ALT (U/L)	30 ± 29
ALP (U/L)	75 ± 36
Albumin (g/dL)	4.3 ± 0.4
AFP (mg/dL)	18 (1.3–200,000)
PIVKA-II (mAU/mL)	79 (8–75,000)
ICG-R15 (%)	10.1 ± 5.5
Preoperative PET CT (positive)	258 (61.4%)
Perioperative and pathologic	
Extent of hepatectomy (major)	176 (42.2%)
Laparoscopic liver resection	68 (16.2%)
Maximum tumor size ≥ 5 cm	141 (33.6%)
Tumor number (multiple)	45 (10.7%)
Tumor grade III or IV	107 (25.5%)
Tumor hemorrhage	222 (52.9%)
Tumor necrosis	186 (44.3%)
Encapsulation	379 (90.2%)
Microvascular invasion	238 (56.7%)
PVTT	33 (7.9%)
BDTT	13 (3.1%)
Serosal involvement	10 (2.4%)
Intrahepatic metastasis	46 (10.9%)
Multicentric occurrence	21 (5.0%)
Cirrhosis	167 (39.8%)
Tumor-free resection margin (mm)	10 ± 13

HBV hepatitis B virus, *NLR* neutrophil–lymphocyte ratio, *NMR* neutrophil–monocyte ratio, *AST* aspartate transaminase, *ALT* alanine transaminase, *ALP* alkaline phosphatase, *AFP* alpha-fetoprotein, *PIVKA-II* protein induced by vitamin K absence/antagonism-II, *ICG-R15* indocyanine green retention rate at 15 min, *PET* positron emission tomography, *PVTT* portal vein tumor thrombosis, *BDTT* bile duct tumor thrombosis

Outcomes

The mean follow-up duration after hepatectomy was 42 ± 21 months. One hundred fifty patients (35.7%) developed recurrent HCC by the last visit. Intrahepatic recurrence and extrahepatic recurrence occurred in 126 (84.0%) and 21 patients (14.0%), respectively. Three patients developed concurrent intrahepatic and extrahepatic recurrence. For all patients, the 1-year, 3-year, and 5-year RFS rates and OS rates were 74.9%, 65.4%, and 60.2% and 97.6%, 94.4%, and 91.7%, respectively. The risk factors for predicting HCC recurrence are listed in Table 2; aspartate transaminase (AST) ≥ 27 U/mL, alanine transaminase (ALT) ≥ 27 U/mL, alanine phosphatase (ALP) ≥ 68 U/mL, albumin < 4.0 mg/dL, PIVKA-II ≥ 217 mAU/mL, laparoscopic liver resection, tumor size > 5 cm, multiple tumors, tumor necrosis, microvascular invasion, PVTT, BDTT, intrahepatic metastasis, multicentric occurrence, and tumor-free resection margin < 4 cm were associated with poor RFS. Multivariate analysis showed that ALP ≥ 68 U/mL, albumin < 4.0 mg/dL, PIVKA-II ≥ 217 mAU/mL, multiple tumors, absence of tumor hemorrhage, PVTT, intrahepatic metastasis, and tumor-free resection margin < 4 cm were predisposing factors for HCC recurrence.

Univariate analysis showed that increased platelet count, AST ≥ 61 IU/mL, ALT ≥ 24 IU/mL, ALP ≥ 71 IU/mL, AFP ≥ 26.7 mg/dL, PIVKA-II ≥ 95 mAU/mL, preoperative positive PET/CT, tumor size ≥ 5 cm, multiple tumors, absence of encapsulation, tumor necrosis, microvascular invasion, PVTT, BDTT, intrahepatic metastasis, and multicentric occurrence were closely associated with patient survival (Table 3). Tumor size ≥ 5 cm, multiple tumors, and serum ALT ≥ 24 IU/mL were closely associated with patient death on multivariate analysis.

Nomogram Success in Predicting HCC Recurrence and Patient Survival

We made nomograms that predicted RFS and OS by combining significant factors from the multivariate analysis (Fig. 1) In our internal validations, the bootstrap-corrected *C*-indices were 0.703 (95% CI, 0.701 to 0.704) and 0.810 (95% CI, 0.807 to 0.813) for the RFS and OS prognostic nomograms, respectively, which indicate considerable predictability (Fig. 2). The actual survival probability and the predicted survival probability were correlated for 1-year, 3-year, and 5-year survival for both RFS and OS and were well matched along an ideal 45-degree line.

Discussion

The decision to perform surgical liver resection for HCC depends on tumor location, extent, size, patient comorbidities, and residual liver function after surgery. Using data from our series of patients who underwent curative liver resection, we created predictive nomograms using Cox regression models that predict individual patient HCC recurrence and survival after surgery. These easy-to-use graphical nomograms consist of ordinary clinical variables, including preoperative and pathological characteristics.

Several conventional staging systems use tumor diameter and tumor number as variables for tumor classification.[1,5,20]

Table 2 Risk factors for HCC recurrence

	Univariate			Multivariate (stepwise)		
	OR	95% CI	*p*	OR	95% CI	*p*
Gender (male)	1.103	0.735–1.653	0.637			
Age	0.975	0.952–1.005	0.107			
Positive HBV DNA	1.122	0.853–1.480	0.389			
Neutrophil count	1.055	0.950–1.172	0.314			
Lymphocyte count	0.921	0.711–1.194	0.536			
NLR	0.864	0.489–1.525	0.614			
NMR	0.566	0.034–9.320	0.690			
Hemoglobin	0.965	0.877–1.062	0.466			
Platelet	1.001	0.999–1.003	0.369			
AST ≥ 27 U/L	1.589	1.110–2.276	0.012			
ALT ≥ 27 U/L	1.724	1.225–2.426	0.002			
ALP ≥ 68 U/L	2.231	1.502–3.313	< 0.001	1.832	1.197–2.804	0.005
Albumin < 4 g/dL	2.014	1.368–2.965	< 0.001	2.064	1.346–3.164	< 0.001
AFP ≥ 23.4 mg/dL	1.272	0.914–1.770	0.153			
PIVKA-II ≥ 217 mAU/mL	2.167	1.550–3.032	< 0.001	2.073	1.452–2.960	< 0.001
ICG-R15	1.004	0.975–1.004	0.783			
Preoperative PET CT (positive)	0.884	0.639–1.223	0.455			
Extent of hepatectomy (major)	1.041	0.750–1.446	0.809			
Laparoscopic liver resection	0.487	0.281–0.845	0.011			
Tumor size ≥ 5 cm	1.976	1.431–2.728	< 0.001			
Tumor number (multiple)	2.805	1.878–4.190	< 0.001	2.126	1.311–3.449	0.002
Tumor grade III or IV	1.227	0.853–1.764	0.271			
Tumor hemorrhage	0.765	0.555–1.055	0.102	0.658	0.464–0.932	0.018
Tumor necrosis	1.715	1.244–2.365	0.001			
Encapsulation	0.604	0.377–0.968	0.036			
Microvascular invasion	2.252	1.587–3.196	< 0.001			
PVTT	3.750	2.380–5.909	< 0.001	1.996	1.157–3.441	0.013
BDTT	1.678	0.785–3.586	0.182			
Serosal involvement	2.027	0.896–4.589	0.090			
Intrahepatic metastasis	3.299	2.217–4.909	< 0.001	1.946	1.156–3.276	0.012
Multicentric occurrence	2.154	1.219–3.805	0.008			
Cirrhosis	0.951	0.684–1.321	0.762			
Tumor-free resection margin < 4 cm	2.778	1.029–7.502	0.044	5.155	1.613–16.470	0.006

HBV hepatitis B virus, *NLR* neutrophil–lymphocyte ratio, *NMR* neutrophil–monocyte ratio, *AST* aspartate transaminase, *ALT* alanine transaminase, *ALP* alkaline phosphatase, *AFP* alpha-fetoprotein, *PIVKA-II* protein induced by vitamin K absence/antagonism-II, *ICG-R15* indocyanine green retention rate at 15 min, *PET* positron emission tomography, *PVTT* portal vein tumor thrombosis, *BDTT* bile duct tumor thrombosis

However, these two factors are insufficient to predict the postoperative course for hepatectomy patients because they cannot reflect the biological characteristics of HCC. Although a reliable conventional staging system is widely used, the clinical and pathologic variables affecting prognosis vary and are not sufficiently predicted by currently used systems.

Nomograms are individualized and highly accurate for prognostic estimation; they have been widely developed for various malignancies.[6,7,9,10,21–23] The concordance index and calibration figure for each nomogram are reliable statistical tools for evaluating cancer staging systems.[6] More importantly, nomograms can improve the prognostic function of staging systems at both group and individual levels. Nomograms are visualizations of quantized risk variables and are useful for surgeons and patients to better understand short- and long-term outcomes. In this study, we developed a nomogram for predicting HCC recurrence and patient survival based on preoperative and pathologic data in HCC patients.

In a cirrhotic liver, HCC may occur after inflammation, regeneration, or liver fibrosis.[24] Pathogenesis of HCC by

Table 3 Risk factors for death

	Univariate			Multivariate (stepwise)		
	OR	95% CI	*p*	OR	95% CI	*p*
Gender (male)	0.751	− 0.318–1.776	0.515			
Age	0.918	0.977–1.190	0.342			
Positive HBV DNA	1.044	0.489–1.988	0.833			
Neutrophil count	1.191	0.959–1.479	0.114			
Lymphocyte count	1.025	0.535–1.963	0.940			
NLR	0.362	0.085–1.553	0.171			
NMR	0.085	0.000–97.608	0.493			
Hemoglobin	1.086	0.862–1.369	0.483			
Platelet	1.005	1.001–1.008	0.010			
AST ≥ 61 U/L	2.612	1.052–6.482	0.038			
ALT ≥ 24 U/L	13.559	1.840–99.920	0.011	9.525	1.276–71.130	0.028
ALP ≥ 71 U/L	3.190	1.208–8.425	0.019			
Albumin	0.855	0.331–2.208	0.746			
AFP ≥ 26.7	2.385	1.011–5.627	0.047			
PIVKA-II ≥ 95 mAU/mL	5.514	1.876–16.212	0.002			
ICG-R15	0.926	0.849–1.010	0.082			
Preoperative PET CT (positive)	0.284	0.124–0.651	0.003			
Extent of hepatectomy (major)	1.735	0.800–3.761	0.163			
Laparoscopic liver resection	0.095	0.005–1.634	0.105			
Tumor size ≥ 5 cm	7.536	3.041–18.680	< 0.001	5.095	1.981–13.110	< 0.001
Tumor number (multiple)	7.861	3.691–16.744	< 0.001	3.841	1.737–8.493	< 0.001
Tumor grade III or IV	1.716	0.763–3.861	0.192			
Tumor hemorrhage	1120	0.524–2.393	0.770			
Tumor necrosis	3.314	1.448–7.584	0.005			
Encapsulation	0.364	0.147–0.902	0.029			
Microvascular invasion	6.636	1.997–22.050	0.002			
PVTT	2.966	1.121–7.844	0.029			
BDTT	3.664	1.101–12.193	0.034			
Serosal involvement	1.702	0.231–12.547	0.602			
Intrahepatic metastasis	4.036	1.812–8.991	< 0.001			
Multicentric occurrence	3.515	1.215–10.168	0.020			
Cirrhosis	0.870	0.398–1.901	0.728			
Tumor-free resection margin < 4 cm	1.580	0.214–11.683	0.654			

HBV hepatitis B virus, *NLR* neutrophil-lymphocyte ratio, *NMR* neutrophil-monocyte ratio, *AST* aspartate transaminase, *ALT* alanine transaminase, *ALP* alkaline phosphatase, *AFP* alpha-fetoprotein, *PIVKA-II* protein induced by vitamin K absence/antagonism-II, *ICG-R15* indocyanine green retention rate at 15 min, *PET* positron emission tomography, *PVTT* portal vein tumor thrombosis, *BDTT* bile duct tumor thrombosis

HBV infection is not thoroughly understood because it follows a complicated process and could be related to virus-induced inflammation and regeneration. However, HCC may also develop as a direct effect of the virus through integration of HBV DNA into the DNA of infected hepatocytes.[25] The range of NLR in our study was 0.05 to 1.74 because the incidence of patients with non-cirrhotic liver was 58.9%. A preoperative positive PET finding is a powerful predictor of prognosis in HCC patients.[26] Tumor recurrence in most gastrointestinal cancers involves not only local recurrence but also multiple metastases in remote areas. Because tumor recurrence patterns between HCC and other gastrointestinal cancers are different, PET/CT cannot accurately predict prognosis after curative liver resection in HBV-related HCC patients. Preoperative PET/CT evaluation is not commonly used in other countries but is covered by national insurance in Korea; thus, preoperative PET/CT evaluation is routinely used in our country.

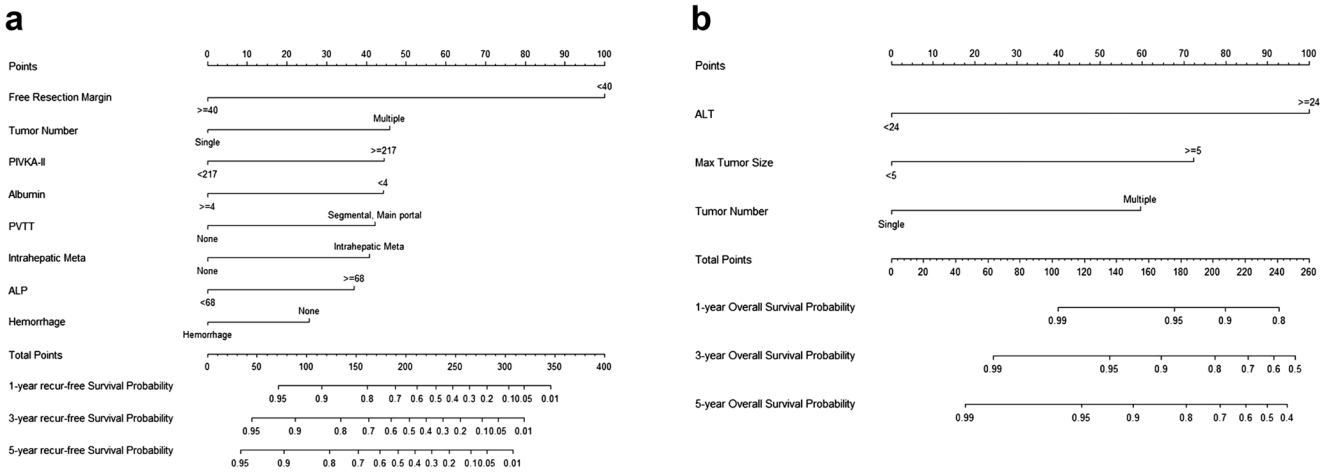

Fig. 1 Relapse-free survival (**a**) and overall survival (**b**) nomograms

A previous study created a novel prognostic nomogram to predict recurrence-free survival (*C*-index = 0.67) and patient survival (*C*-index = 0.74) after hepatic resection and reported superior prediction compared with numerous other staging systems.[7] Torzilli et al. reported that the *C*-index values of overall and disease-free survival were 0.62 and 0.61, respectively.[27] Another study reported sex, serum albumin, platelet count, microvascular invasion, and calculated tumor volume as independent predictors. It also estimated *C*-index values for 2-year recurrence and 5-year disease-free survival as 0.66 and 0.67, respectively.[28]

Our *C*-index values (*C*-index for RFS = 0.712 and *C*-index for OS = 0.819) were statistically higher than those estimated by the Liver Cancer Study Group of Japan (*C*-index = 0.64), the American Joint Committee on Cancer (AJCC) seventh edition (*C*-index = 0.65), the BCLC classification (*C*-index = 0.52), and the nomogram recently proposed by Shim et al. (*C*-index = 0.67).[27,28] Previously published studies on nomograms for HCC have an important limitation; they included the three main etiologies for HCC: HBV, HCV, and alcohol use. However, our cohort study included only patients with HBV-related HCC.

Our postoperative nomograms were more accurate for predicting prognosis than other conventional staging systems because they were based on personalized preoperative and postoperative data. Furthermore, our study focused in hepatectomy patients with treatment-naïve HBV-related HCC. The high predictive accuracy of postoperative outcomes is due to inclusion of a relatively sufficient number of prognostic factors associated with tumor size, tumor number, tumor grade, tumor hemorrhage, tumor necrosis, microvascular invasion, portal vein tumor thrombosis, preoperative PET/CT, tumor-free resection margin, and encapsulation. Our study included only treatment-naïve HBV-related HCC patients and

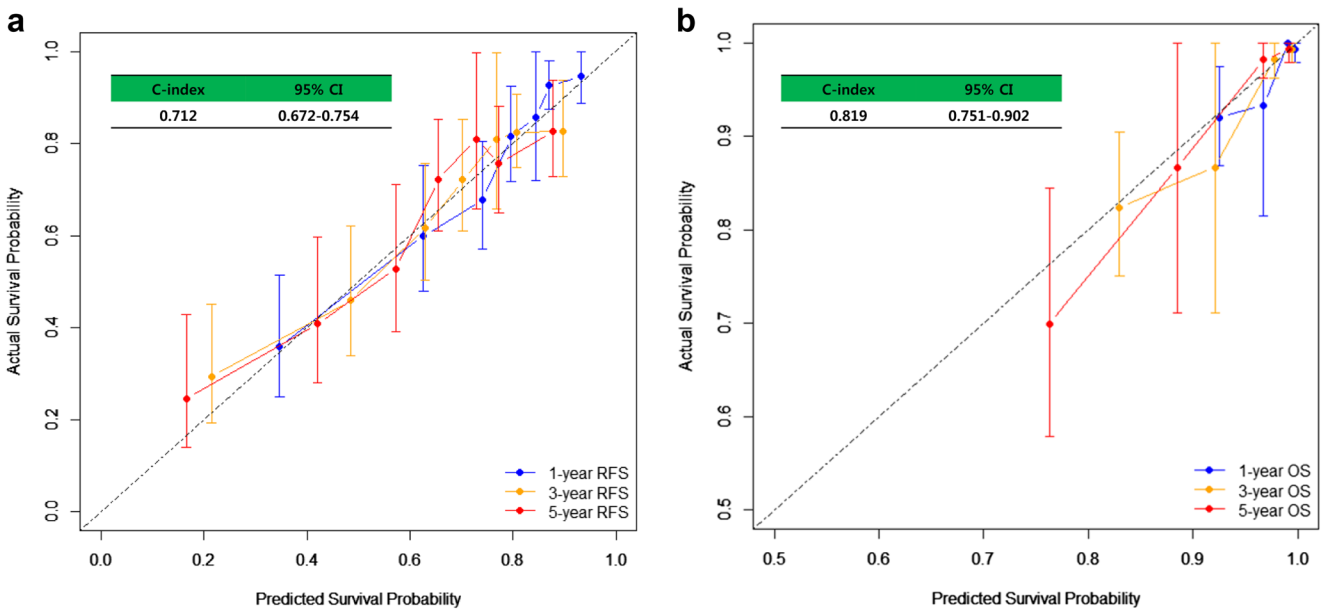

Fig. 2 Calibration curves for predicting 1-year, 3-year, and 5-year. Left side image is relapse-free survival (**a**) and right side image is overall survival (**b**)

evaluated the effect of preoperative PET/CT. These two features of this study are different from previous studies. Patients with suspected poor prognosis based on a nomogram should first undergo transarterial radioembolization (TARE) or other treatments such as TACE, RFA, or radiation. Surgical liver resection should be considered in patients with favorable tumor biology or good treatment response. Additionally, our novel model can be used to guide postoperative monitoring and design of clinical trials based on prognostic stratification.

Our study has several limitations. First, it is retrospective and thus may contain unavoidable selection bias. Second, our nomograms were mainly based on hepatectomy patients with preoperative radiologically HBV-related HCC and well-preserved liver function, which introduces further selection bias. Third, this study was dependent on a single institutional cohort of patients from Korea. HBV is the most common cause of HCC in Korea. Prospective multicenter studies are required to validate the prognostic accuracy shown herein. Fourth, our study does not include HCC molecular studies, limiting its potential for use in targeted and personalized therapies.

Conclusion

We established two prognostic nomograms to predict RFS and OS in hepatectomy patients with treatment-naïve HBV-related HCC. Through these prognostic models, surgeons and physicians can precisely predict HCC recurrence or survival of individual HCC patients after curative hepatic resection. Further studies on the effectiveness and reliability of these predictive models are needed.

Authors' contributions JMK: Design, literature search, data acquisition, analysis, interpretation, and writing.
JWJ: Design and data interpretation.
HY and KK: Data analysis.
GSC, CHDK, DHS, and JHL: Acquisition and analysis of data.
All authors read and agree with the manuscript.

Compliance with Ethical Standards

Competing Interests The authors declare that they have no conflicts of interest.

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